Signals That Foster Pancreatic Development

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Understanding the spatial and temporal requirements of crucial factors for endocrine progenitor specification, proliferation, and terminal differentiation remains a major challenge in the field of pancreas development. Over the past several years, a network of transcription factors has been identified that are required to generate the different pancreatic cell lineages. Our laboratory has focused on two of these, *p*ancreatic *d*uodenal *homeobox 1* (*pdx1*) and *h*epatic *n*uclear *f*actor *6* (*HNF6*). Both of these genes are expressed broadly in the pancreatic bud epithelium early in development; however, at the time when islets begin to form, the expression patterns of *pdx1* and *HNF6* diverge, such that *pdx1* becomes highly enriched in insulin-producing beta cells, and *HNF6* is down-regulated in endocrine cells only. The current body of evidence indicates that both factors function in early endocrine specification and that *pdx1* is required for the generation and maintenance of mature pancreatic endocrine cells. The precise temporal requirement for *HNF6* in the production of terminally differentiated endocrine cells remains unclear; however, down-regulation of *HNF6* is absolutely essential for mature islet function and morphogenesis. We, and others, have proposed that an understanding of embryonic pancreas development will lead to strategies for inducing beta cell differentiation from ES cells or adult pancreatic stem cells. Recent studies from several laboratories including our own, however, suggest that the mechanisms used for expansion of endocrine mass postnatally differ from pathways used during embryogenesis. Thus, the factors responsible for maintenance and growth of beta cell mass might be targets for regeneration *in vivo* or expansion of beta cells *ex vivo* from adult sources.